ReMuS MULTIPLE SCLEROSIS PATIENT REGISTRY

Regular Output from ReMuS Registry

Data export updated on 31. 12. 2015

– Summary Report

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– Summary Report

Contents

1 Introduction

National Multiple Sclerosis Patient Registry (ReMuS) was mainly created to obtain data on the occurrence, incidence and clinical course of multiple sclerosis (MS), its clinical symptoms, MS relapse frequency rates, disease progression, MS treatment, disability development, comorbidities and causes of death. The objective is to provide outputs for cost and effectiveness monitoring of health care and medicinal preparations, evaluation of information to be provided to health care payers, other public institutions and medicinal preparation manufacturers, further to assess the severity of MS and its socioeconomic impacts, and to facilitate the creation of outputs for scientific and statistical purposes.

Based on acquired data, it will be possible to look for possible risk factors both for the occurrence of MS itself and lack of effectiveness of treatment or more rapid progression of the disease. Information on course of MS will enable health care payers to better plan the financial means necessary for the treatment of this disease. Information on treatment effectiveness are instrumental in improving therapeutic choices and implement changes or modifications when relevant.

The registry now includes, in this first phase, only multiple sclerosis patients who:

- undergo treatment in one of the participating MS treatment centres
- have received one of the DMDs (disease modifying drugs) preparations (i.e. disease progression modifying treatment) or IVIGs (intravenous immunoglobulins) any time after 1.1.2013,
- have signed informed consent with processing their personal and clinical data in ReMuS registry.

More detailed analysis includes only patients who have been entered current visit from the second half of 2015 into the registry.

2 Results

As of 31.12.2015, ReMuS registry included data of patients from thirteen MS treatment centres – General University Hospital in Prague (VFN), Teplice, Jihlava, University Hospital Motol in Prague, University Hospitals in Plzeň, Pardubice, University Hospital in Ostrava, University Hospital Královské Vinohrady, Thomayer University Hospital in Krč, University Hospital in Hradec Králové, University Hospital in Brno (Bohunice), University Hospital in Olomouc and Hospital in České Budějovice. The analysis included data of patients who were treated in the period from 1. 1. 2013 with one of the DMD and IVIG preparations reported below and for whom current data were available:

- DMDs – Aubagio, Avonex, Betaferon, Copaxone[20], Copaxone[40], Extavia, Gilenya,Lemtrada, Rebif[22], Rebif[44], Tecfidera, Tysabri
- IVIGs – Endobulin, Flebogamma, Gammagard, Kiovig, Octagam.

Table 1 gives the final number of patients included in ReMuS registry as of 31. 12. 2015. The first column contains total number of patients in the registry (patients satisfying the condition of informed consent and treatment with DMDs or IVIGs), while the number of patients with current data (last visit in the second half of 2015) who were included in the current analysis is given in the second column.

Table 1 Total number of patients by centres

Centre	Patients in the registry	Analysed patients	Percentage in the analysis
VFN	2067	2009	25,8%
Teplice	767	730	9,4%
Jihlava	244	238	3,1%
Motol	925	887	11,4%
Plzeň	478	471	6,0%
Pardubice	451	439	5,6%
Ostrava	796	792	10,2%
Vinohrady	373	361	4,6%
Krč	283	277	3,6%
Hradec Králové	716	710	9,1%
Brno Bohunice	342	336	4,3%
Olomouc	183	177	2,3%
České Budějovice	368	359	4,6%
Total	7993	7786	100,0%

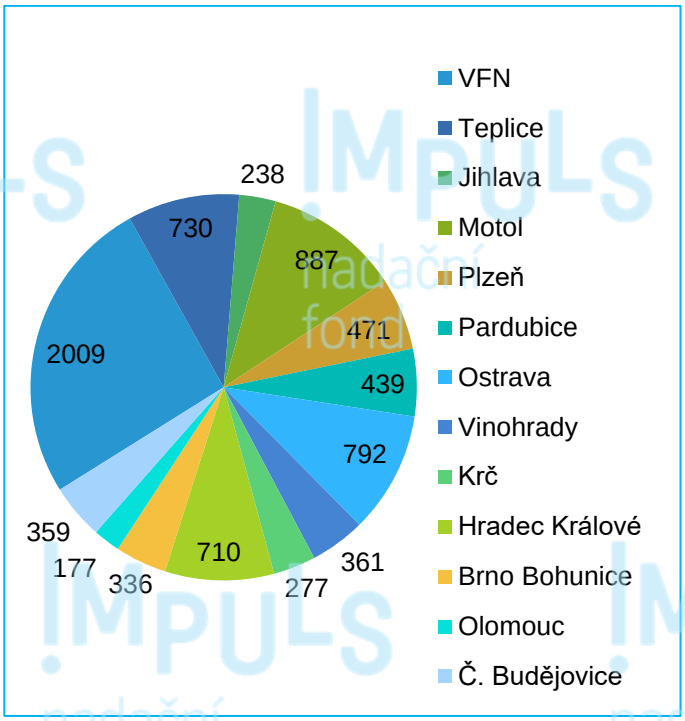

Figure 1 Total number of analysed patients by centres

The table and figure below illustrate the development of the numbers of patients and centres participating in ReMuS registry from the creation of the registry till present. The first data export in summer 2013 analysed data originating from three centres - a total of 1 501 patients. Now, in December 2015, the registry has expanded to include 13 MS treatment centres already, so the data of 7 786 patients from the whole of the Czech Republic enter analysis.

Table 2 Number of patients in the ReMuS registry - development

Data export date	Number of centres	Number of patients to be analysed
30. 6. 2013	3	1501
31. 12. 2013	7	2920
30. 6. 2014	12	4715
31. 12. 2014	12	5639
30. 6. 2015	13	7099
31. 12. 2015	13	7786

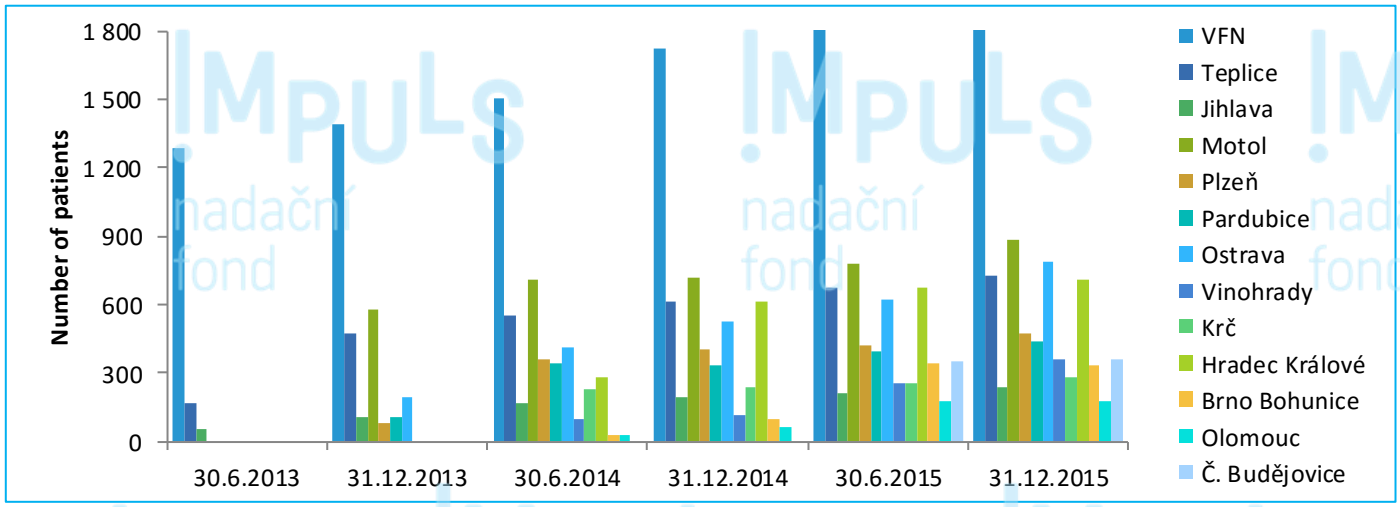

Figure 2 Number of patients in the registry contributed by individual centres - development

2.1 Demographic data

2.1.1 Sex

Taken together, all centres treat 71,7% women and 28,3% men.

Table 3 Patient distribution by sex

Sex	All centres	
	Number	Percentage
Females	5583	71,7%
Males	2203	28,3%

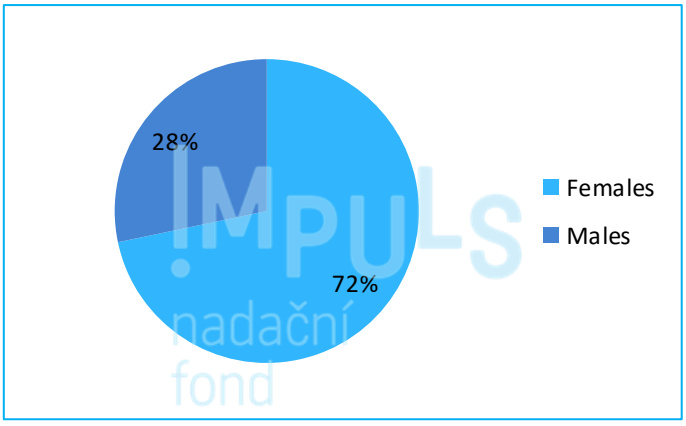

Figure 3 Patient distribution by sex

2.1.2 Age at last patient visit

Mean age at last visit is 40,7 years. For females, mean age was slightly higher than in men. Overall, the registry now includes 32 patients younger than 18 years, and 8 of these are younger than 15 years. When all MS treatment centres are taken together the most represented age group is that of patients aged 30 – 40 years.

Table 4 Patient age in years at last visit

Centre	Mean	Median	Minimum	Maximum	SD	Number of missing values
All centres	40,7	40,1	9,3	78,1	10,2	0

Table 5 Patient age in years at last visit by sex

Centre	Sex	Mean	Median	Minimum	Maximum	SD	Number of missing values
All centres	Females	41,1	40,5	9,6	74,0	10,3	0
	Males	39,9	39,0	9,3	78,1	9,9	0

Table 6 Number of patients younger than 15 and 18 let, respectively

Age	All centres	
	Number	Percentage
< 15 years	8	0,1%
< 18 years	32	0,4%

Table 7 Number of patients in individual groups by decades

Age	All centres	
	Number	Percentage
0 – 10	2	0,0%
10 – 20	71	0,9%
20 – 30	1154	14,8%
30 – 40	2625	33,7%
40 – 50	2423	31,1%
50 – 60	1203	15,5%
60 – 70	296	3,8%
70 – 80	12	0,2%
80 – 90	0	0,0%
90 – 100	0	0,0%

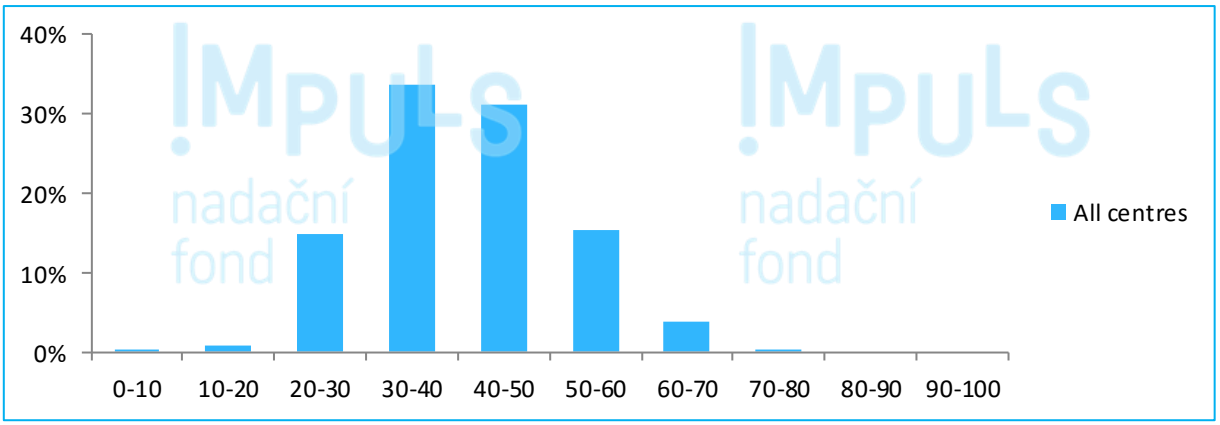

Figure 4 Patient distribution by age

2.1.3 Age at disease onset

Date of disease onset is an important parameter that is used to calculate patient age at disease onset and disease duration period. This parameter was missing for 26 patients.

Mean age at disease onset is 30,5 years. Table 8 shows, however, that patient age at disease onset ranged from below 4 years to 67 years.

Table 8 Patient age in years at the time of disease onset

Centre	Mean	Median	Minimum	Maximum	SD	Number of missing values
All centres	30,5	29,3	3,5	67,3	9,5	26

2.1.4 Patient distribution by individual healthcare insurance companies

Table 9 and Figure 5 show the distribution of patients in the registry by individual health insurance companies. 58,0% patients are insured with the General Health Insurance Company (code: 111). 13,3% are insured with Health Insurance Company of the Ministry of Internal Affairs (code: 211) and 9,9% with Business Health Insurance Company (code: 207).

Table 9 Patient distribution by health insurance companies

Health Insurance Co.	All centres	
	Number	Percentage*
111	4516	58,0%
201	424	5,4%
205	695	8,9%
207	774	9,9%
209	123	1,6%
211	1037	13,3%
213	212	2,7%
Other	3	0,0%

* 2 patients (0,0%) had no data entered for health insurance company

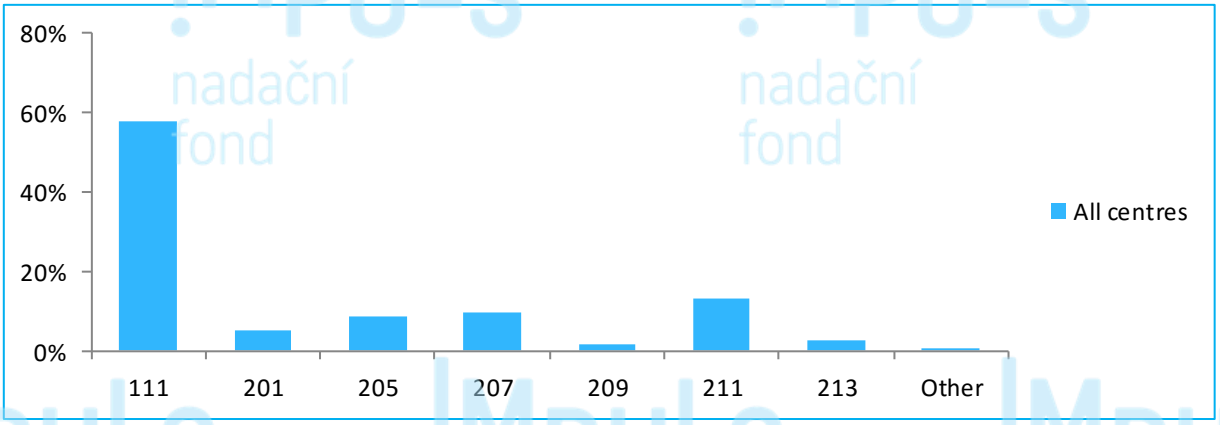

Figure 5 Patient distribution by health insurance companies

2.1.5 Patient distribution by regions

The registry makes it possible to obtain data on patient distribution by individual Czech Republic regions based on ZIP codes attached to patient residence addresses. ZIP codes assigned to communities that were part of two regions were assigned to the region that included most of the included communities. ZIP codes not found in the ZIP code registry of the Czech National Postal Office (Czech Post) were interpreted as incorrect.

The registry includes patients from all Czech Republic regions.

Table 10 Patient distribution by regions of their residence

Regions	All centres	
	Number	Percentage*
South Bohemia	519	6,7%
South Moravia	308	4,0%
Karlovy Vary	210	2,7%
Vysočina	429	5,5%
Hradec Králové	534	6,9%
Liberec	339	4,4%
Moravia-Silesia	752	9,7%
Olomouc	176	2,3%
Pardubice	535	6,9%
Plzeň	407	5,2%
Prague	1546	19,9%
Central Bohemia	1284	16,5%
Ústí nad Labem	606	7,8%
Zlín	137	1,8%

* 2 patients did not have completed residence addresses and 2 patients have residence in Slovakia

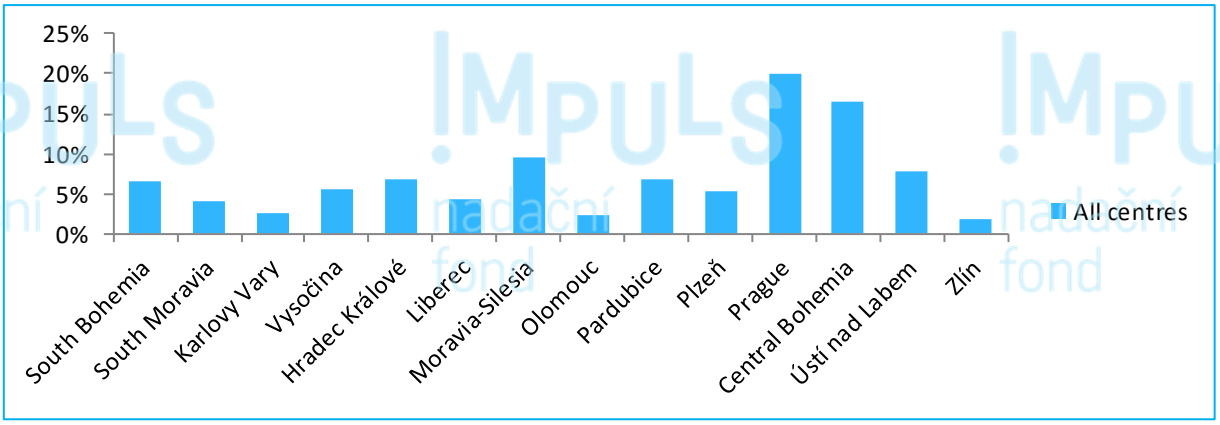

Figure 6 Patient distribution regions of their place of residence

2.2 Employment and social benefits

Employment and provision of social benefits are evaluated based on data obtained at last visit. These parameters must be completed at each visit even when the condition remains the same.

It should be noted that all possibilities and combinations of employment and especially those for social benefits cannot be appreciated and the clarity and purposefulness of the output is preserved at the same time. It was thus necessary to introduce certain preference criteria so the physicians be able to complete the data and decide what options to choose in unclear combined cases. These preference criteria (that is that the type of disability pension [DP] takes precedence over unemployment benefits or maternal leave [ML]) must be taken into account when interpreting and presenting this type of data.

2.2.1 Employment

As part of entering employment data, the selection must be made among the options PTE – part-time employment, FTE – full-time employment, DNW – does not work (irrespective of the reasons for employment/unemployment and possible social benefits) and STUDENT – studies (social and health insurance is paid for by the state).

More than one half of the patients have full-time employment (55,7%), followed by 13,3% patients who work part-time.

Table 11 Patient distribution by employment

Employment	All centres	
	Number	Percentage*
PTE	1034	13,3%
FTE	4338	55,7%
DNW	1861	23,9%
STUDENT	223	2,9%

* 4,2% patients did not have data on employment correctly completed

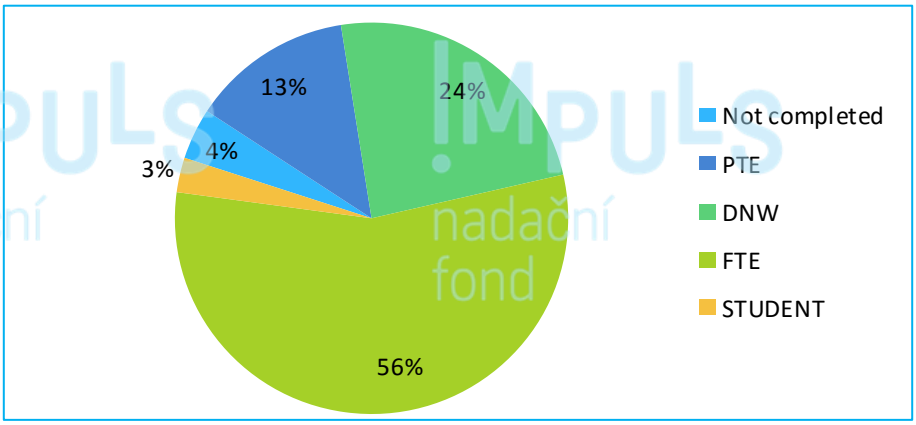

Figure 7 Patient distribution by employment type

2.2.2 Social benefits

The structure of social benefits is based on simplified data as the completer had always to choose one, "most important" benefit in cases where a patient was receiving more benefits. DP1, DP2 and DP3 are social benefits that were of most interest to us - these codes denote 3 degrees of disability pension. ML – maternity leave is only reported as secondary information, as are unemployment benefits (UNEMPL). OAP codes for old-age pension.

55,0% patients do not receive any social benefit.

Table 12 Patient distribution by type of social benefit

Social benefit	All centres	
	Number	Percentage*
DP1	1033	13,3%
DP2	599	7,7%
DP3	882	11,3%
ML	437	5,6%
UNEMPL	79	1,0%
OAP	142	1,8%
Does not receive (X)	4284	55,0%

* 4,2% patients had no data completed for social benefits

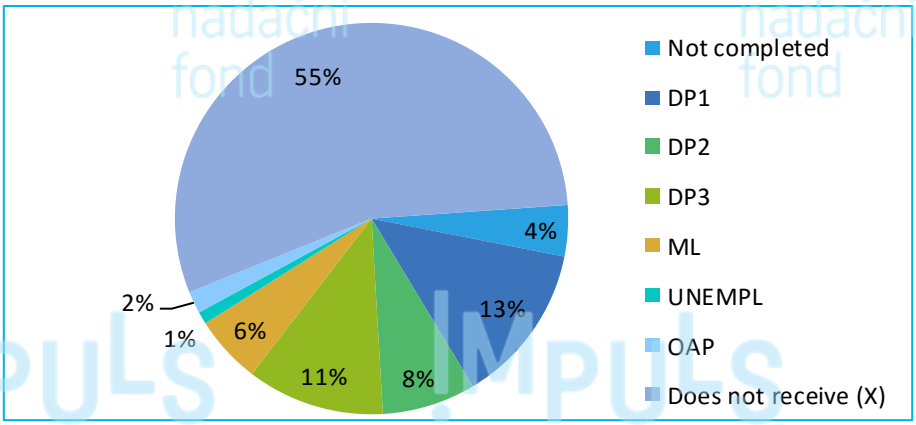

Figure 8 Patient distribution by type of social benefit

2.3 Disease duration period

Mean disease duration period is 10,2 years.

Table 13 Disease duration period (from disease onset to last visit)

Centre	Mean	Median	Minimum	Maximum	SD	Number of missing values
All centres	10,2	8,6	0,1	45,4	7,5	26

2.4 Degree of damage

Degree of damage is assessed using EDSS (Expanded Disability Status Scale) assigned value at each visit. Degree of damage is analysed as that found at the last available patient visit.

EDSS ranges from 0 to 10, where 0 means healthy patient without complaints, degree 5 corresponds to considerable damage, inability to work and ability to walk for a distance less than 500 metres, and degree 10 means death due to MS.

Median EDSS value is 2,5. Most patients are in the EDSS group between 1,5 – 2.

Table 14 Degree of damage (EDSS value) at last visit

Centre	Mean	Median	Minimum	Maximum	SD	Number of missing values
All centres	2,7	2,5	0,0	8,0	1,5	13

Table 15 Degree of damage (EDSS value) at last visit

EDSS	All centres	
	Number	Percentage*
0 – 1	1101	14,1%
1,5 – 2	2809	36,1%
2,5 – 3	1368	17,6%
3,5 – 4	1162	14,9%
4,5 – 5	746	9,6%
5,5 – 6	429	5,5%
6,5 – 7	144	1,8%
7,5 – 8	14	0,2%
8,5 – 9	0	0,0%
9,5 – 10	0	0,0%

* 0,2% patients had no data completed about EDSS degree

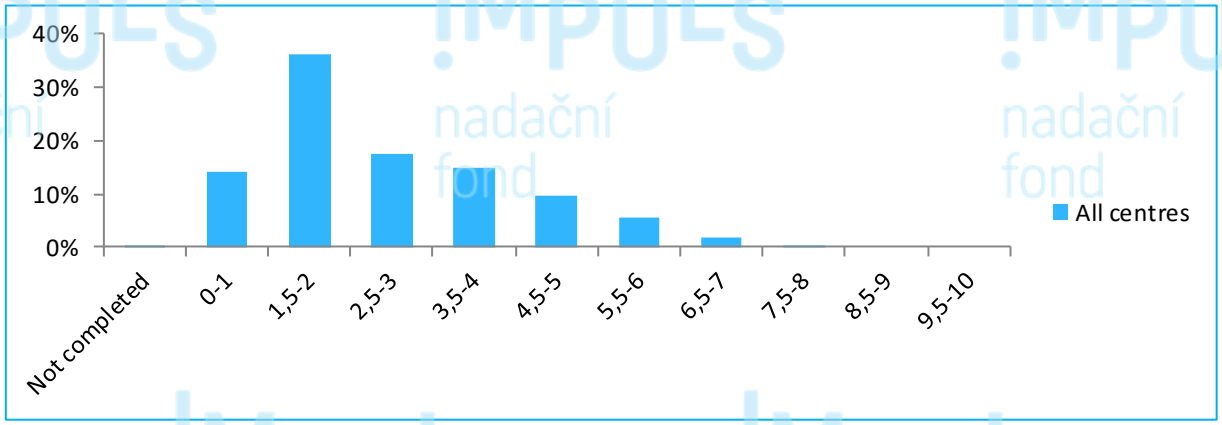

Figure 9 Patient distribution by EDSS degree

2.5 Relapse

Over the last 6 months, relapse of the disease (recurrence of symptoms) was recorded in 10,4% patients, and 27,0% over the period of 12 months. What should be taken into account is that the number of relapses reported here is an overall number including multiple relapses in one patient. Mean number of relapses annually (ARR, annualized relapse rate) is 0,270.

Table 16 Relapse occurrence over last 6 and 12 months

Relapse	All centres	
	Number	Percentage
Over 6 months	807	10,4%
Over 12 months	2099	27,0%

Relapse severity is defined as mild, moderate or severe. Mild relapse intensity means that the relapse does not impact negatively on activities of daily life (ADLs). Moderate intensity does impact on activities of daily life already, while the severe form is recorded in cases where the relapse is associated with severe discomfort of the patients, deteriorates their activities of daily life significantly and results in their inability to work, or hospital admission.

Severity of most relapses was mild or moderate. Mild relapses account for 50,4% of all recorded relapses over the last 6 months, while this rate is 50,7% over the last 12 months. Moderate-intensity relapses was 44,4%, or 44,1% and severe relapses was 3,7%, or 4,0%.

Table 17 Relapse severity over last 6 and 12 months

Relapse	All centres	
over 6 months	Number	Percentage*
Mild	407	50,4%
Moderate	358	44,4%
Severe	30	3,7%
Relapse		
over 12 months	Number	Percentage*
Mild	1065	50,7%
Moderate	926	44,1%
Severe	85	4,0%

* In 1,5% of the recorded relapses data on relapse severity over last 6 months were missing
In 1,1% of the recorded relapses data on relapse severity over last 12 months were missing

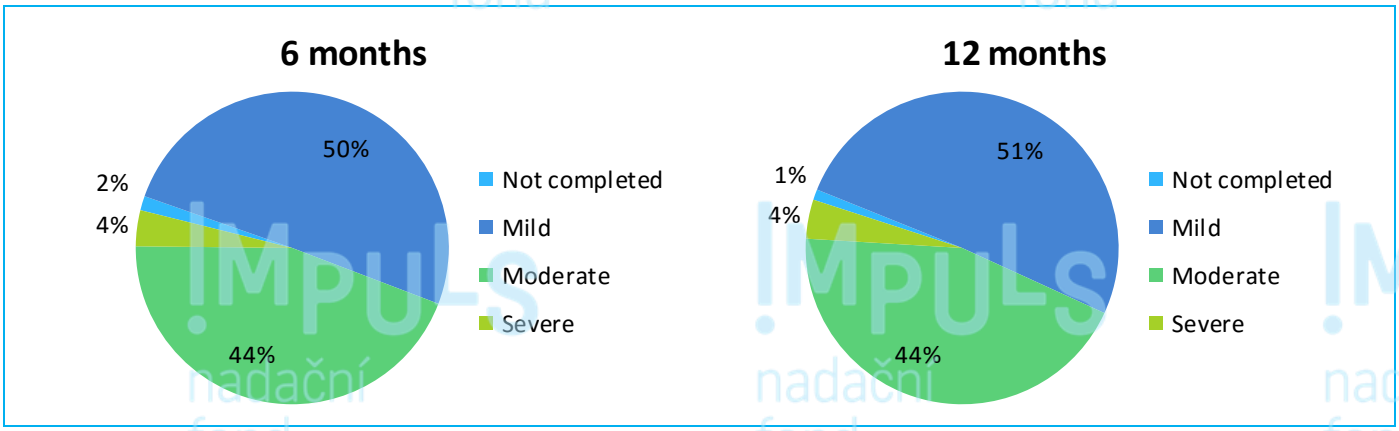

Figure 10 Relapse severity over last 6 and 12 months

The last analysed parameter was the form of relapse treatment – outpatient vs. inpatient treatment. Vast majority of the relapses was treated on outpatient basis. Rates of hospital treatments in individual centres were up to 10 percent.

Table 18 Type/form of relapse treatment over last 6 and 12 months

Relapse over 6 months	All centres	
	Number	Percentage*
Outpatient	743	92,1%
Hospital stay	45	5,6%
Relapse over 12 months	**All centres**	
	Number	Percentage*
Outpatient	1894	90,2%
Hospital stay	156	7,4%

* 2,4% of relapses recorded over the last 6 months data on type of treatment were missing
2,3% of relapses recorded over the last 12 months data on type of treatment were missing

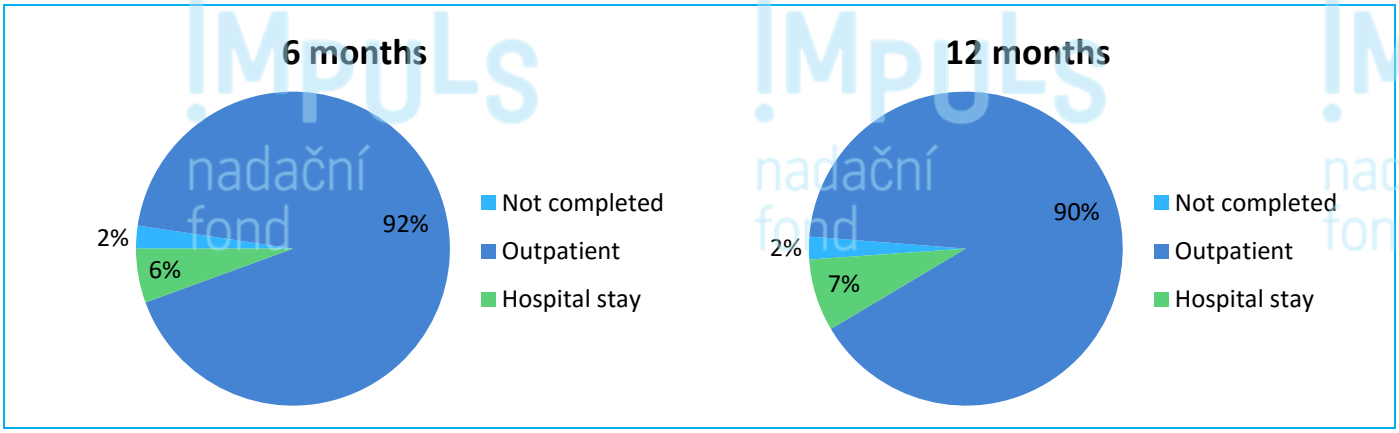

Figure 11 Type/form of treatment over last 6 and 12 months

2.6 Treatment

Evaluation of MS treatment included the preparation used at last visit, a DMD or IVIG. Seven patients did not terminate their treatment for 2 preparations, so the numbers for these patients are included twice. In some cases, it is a parallel treatment with two medicines. It is, however, mostly due to erroneous input into the system (these duplicities will be removed from the registry in the future).

Patients receiving IVIG preparations were included by very few centres in this phase. 335 patients (4,3%) did not receive any DMD or IVIG preparation at their last visit (their treatment was temporarily or permanently discontinued). These 335 patients are not included in Table 19, but are included in Table 20.

Most patients received Avonex (18,5%) or Copaxone [20] (18,1%).

Table 19 Patient distribution by the preparation used at last visit

Treatment	All centres	
	Number	Percentage
DMD		
Aubagio	219	2,9%
Avonex	1378	18,5%
Betaferon	729	9,8%
Copaxone [20]	1348	18,1%
Copaxone [40]	337	4,5%
Extavia	188	2,5%
Gilenya	672	9,0%
Lemtrada	6	0,1%
Rebif[22]	605	8,1%
Rebif[44]	875	11,7%
Tecfidera	248	3,3%
Tysabri	690	9,3%
IVIG	1	0,0%
Endobulin	0	0,0%
Flebogamma	97	1,3%
Gammagard	7	0,1%
Kiovig	47	0,6%
Octagam	11	0,1%

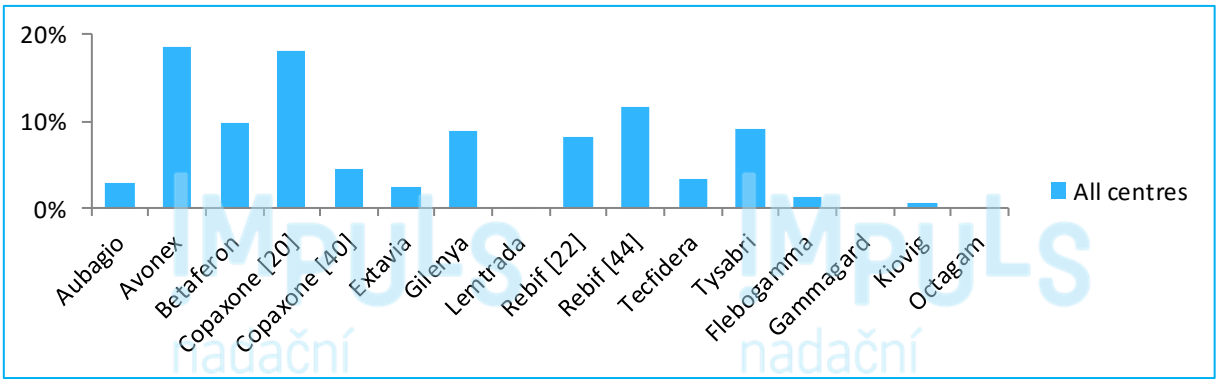

Figure 12 Medicinal preparations used - DMDs and IVIGs

2.6.1 New initiations, terminations or change of therapy with DMDs/ IVIGs

As part of a more detailed analysis of patient treatment the proportion of patients was determined who initiated treatment with new DMD/ IVIG preparations over the last half year and whole year prior to data export on 31. 12. 2015. 3,9% or 8,2% initiated treatment with these preparations, respectively.

The number of patients who terminated treatment with DMDs over the period of interest cannot be exactly determined at present. At their last visit, 335 patients (4,3%) received no treatment. 101 of these patients terminated/discontinued treatment over the half year of interest, and the remaining 234 patients had terminated treatment earlier and did not initiate new treatment over the period of interest.

The last recorded parameter was the number of patients who changed their DMD or IVIG preparation over the period of interest. Over the last half year, the number of these patients was 8,8% while it was 15,4% over the last year.

Table 20 Number of patients who initiated new treatment with DMDs/ IVIGs, terminated or changed these preparations over the period of interest

Treatment - over last 6 months	All centres	
	Number	Percentage
Initiation	300	3,9%
New termination	101	1,3%
Earlier termination	234	3,0%
Termination overall	335	4,3%
Change	685	8,8%
Treatment - over last 12 months	**Number**	**Percentage**
Initiation	638	8,2%
New termination	191	2,5%
Earlier termination	144	1,8%
Termination overall	335	4,3%
Change	1197	15,4%

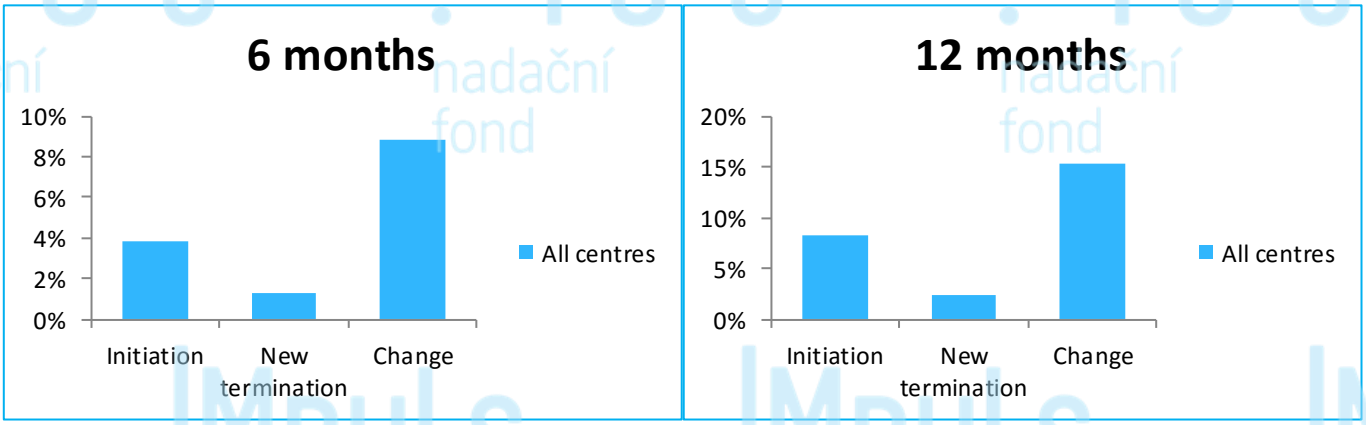

Figure 13 New initiation, termination or change of therapy with DMDs

2.7 Health-related events

2.7.1 Pregnancy

Over the evaluated period of 6 months prior to data export on 31.12.2015 a total of 55 MS patients delivered children (1,0%). 52 of these gave birth to 1 child, 1 patient had twins, and 2 patients did not completed the number of delivered children. In the course of whole 2015 child deliveries were reported in a total of 119 patients (2,1%). 112 of these patient delivered 1 child, 5 patients had twins, and 2 patients had missing data on the number of delivered children.

Table 21 Number of delivered children born over the period of interest

Pregnancies - last 6 months	All centres	
	Number	Percentage
Number of deliveries	55	1,0%
Pregnancies - last 12 months	Number	Percentage
Number of deliveries	119	2,1%

2.7.2 Adverse events

Very few adverse events were recorded. Some centres had not yet started to complete this parameter in more detail. These results cannot thus be reliably interpreted so far. There is still no correction in place for data expression in percentages for the case of multiple AEs in one patient.

In 2015 there was reported a suspicion of one severe health-related event, specifically Copaxone[20]. It was an anaphylaxis. In accordance with informations from MS centre were data reported to the SÚKL (State Institute for Drug Control).

Table 22 Number of adverse events with first occurrence in the period of interest

Number of adverse events - last 6 month	All centres	
	Number	Percentage
Number of AEs	97	1,2%
Number of predefined AEs	30	0,4%
Number of severe AEs	1	0,0%
Number of adverse events - last 12 month	Number	Percentage
Number of AEs	228	2,9%
Number of predefined AEs	83	1,1%
Number of severe AEs	1	0,0%

3 Conclusion

On 31.12.2015, the fourth data export into ReMuS registry was delivered, followed by interim data analysis from the registry focusing on the period from 1. 1. 2015 to 31. 12. 2015. Over the evaluated period data from thirteen MS treatment centres included in ReMuS registry were available - General University Hospital in Prague (VFN), from Teplice, Jihlava, University Hospital in Motol, Prague, Pardubice, University Hospital in Olomouc, University Hospital Královské Vinohrady, Thomayer Hospital in Krč, University Hospital Hradec Králové, University Hospital in Brno (Bohunice), University Hospital in Olomouc, and Hospital in České Budějovice. These centres enter data on their patients in the registry on continual basis, and as of the day of export on 31. 12. 2015 data on treatment of 7 993 patients was available. After the exclusion of patients with no current data, data of a total of 7 786 patients from the whole Czech Republic entered the analysis.

Of patients included in the registry, 71,7% are women, mean patient age at last visit is 40,7 years and mean age at disease onset is 30,5 years. 99,6% patients were older than 18 years at last visit. 58,0% patients are insured with the General Health Insurance Company. The registry includes data of patients from all regions of the Czech Republic. There was marked improvement of data quality and percentages of completed data for employment and social benefits. 69,0% patients are able to work (they work full-time or part-time) and 32,3% receive degree 1-3 disability pensions. The most represented group in terms of degree of damage are patients with EDSS between 1,5 and 2. Mean number of relapses in one year (ARR, annualized relapse rate) is 0,270. 50,4% relapses over the last 6 months and 50,7% relapses over the last 12 months were of mild severity, and the vast majority of patients were treated as outpatients. Medicinal preparations used most commonly are Avonex (18,5%) and Copaxone [20] (18,1%). During the last 6 month 3,9% of patients started with DMD treatment, 1,3% of patients ended or interrupted the DMD treatment and 8,8% of patients changed DMD treatment. Over the last year 8,2% of patients started with DMD treatment, 2,5% of patients ended or interrupted the DMD treatment and 15,4% changed their DMD treatment. In the course of whole 2015 child deliveries were reported in a total of 119 patients. A suspicion of one severe adverse event related to MS treatment (drug: Copaxone) was recorded over the evaluated period. This event was reported to SÚKL (State Institute for Drug Control).

Data interpretation should consider that individual MS treatment centres started their participation gradually and added new patients slowly. All participating centres complete and correct data based on error reports.

Compared to the first data export in June 2013, the number of patients in the registry has now quintupled, while the number of both erroneous and missing data could be reduced, and last but not least, participation of new centres has accentuated and deepened patient and treatment variability in the Czech Republic.